Pharmacovigilance in the pharmaceutical industry

J. C. C. Talbot[1] & B. S. Nilsson[2]

[1]*Pharmacovigilance, Astra Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH and* [2]*Clinical Drug Safety, Astra AB, S-151 85 Södertälje, Sweden*

Keywords: adverse drug reactions, adverse events, drug safety, pharmaceutical industry, pharmacoepidemiology, pharmacovigilance, risk-benefit

Introduction

Pharmacovigilance has been defined as the process of identifying and responding to drug safety issues [1] and has grown considerably as a discipline over the past 10 to 15 years. An educational survey in 1994 revealed that more than 320 people currently worked in company pharmacovigilance functions in the UK alone [2]. Pharmaceutical companies are international, hence the number of staff working in this field within the industry, particularly in other European countries and the USA, is far greater. A major pharmaceutical company such as Astra has over 100 permanent, experienced staff in pharmacovigilance within its research and development organisation in Sweden and the UK and a similar number in local operating companies worldwide. This development has been driven by an increased recognition of the role of pharmacovigilance, the investigation and marketing of a wider range of diverse medicinal products and more stringent and detailed regulatory requirements. The number of individual reports of possible adverse drug reactions (ADRs) can be considerable, for key marketed products often more than 1000 case reports a year are received worldwide from health care professionals and other sources.

The aims of pharmacovigilance within the industry are essentially the same as those of regulatory agencies; that is to protect patients from unnecessary harm by identifying previously unrecognised drug hazards, elucidating predisposing factors, refuting false safety signals and quantifying risk in relation to benefit. Although the perspectives of companies and the regulatory agencies may be different they now work more and more closely together and share information. However, central pharmacovigilance units in major pharmaceutical companies in many instances are far better resourced and have much greater 'in-house' expertise on the safety of their particular products.

Scientific characteristics

Although now seen as a discipline in its own right, pharmacovigilance is related to a number of scientific disciplines, the most important being clinical medicine, clinical and pre-clinical pharmacology, immunology, toxicology and epidemiology.

The identification and analysis of the safety characteristics of medicines falls into two distinct stages. During the first stage, before marketing, the main methodology is experimental with clinical trials comparing the new treatment to placebo or existing alternative treatments. After introduction of a new medicine into general use, the main safety methodology is observational, i.e. uses data from observation of patients treated in clinical practice rather than from experimental situations. In general, the experimental data are of much higher quality than the observational, with better control of confounding factors. The challenge in pharmacovigilance, therefore, is to analyse and draw well-founded conclusions from observational data collected after marketing. In addition, data from observational epidemiological studies are playing an increasingly important role.

Correspondence: Dr J. C. C. Talbot, Pharmacovigilance, Astra Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH.

Pre-marketing clinical trials

Safety monitoring in clinical trials involves collecting adverse events, laboratory investigations and details of the clinical examination of patients. Pharmacovigilance staff may be involved to varying degrees in all phases of clinical trials, including the planning, execution, data analysis and reporting of safety information. Safety issues from animal pharmacology and toxicology studies, findings in phase I studies, known ADRs with similar drugs, signals from other studies and special patient groups, (e.g. the elderly) need to be addressed. The practice of collecting all adverse events rather than suspected ADRs arose from the failure of clinical trials to detect serious reactions with practolol [3] and after several years experience [4] this is now the approach adopted by companies in most studies. The involvement of pharmacovigilance staff in clinical trials also includes an important responsibility for the expedited reporting of individual cases and safety updates required by the UK Medicines Control Agency (MCA) [5] and other regulatory authorities.

Well conducted clinical trials should be able to identify and characterise common type A (pharmacologically mediated) [6] ADRs, indicate how these are tolerated by patients, determine a relationship between ADRs and dose or plasma concentration and identify pre-disposing (risk) factors if at all possible. These issues will usually be presented and discussed in an integrated safety analysis and clinical expert report in the Marketing Authorisation Application submitted by the company and will be the basis of ADRs, warnings and precautions included in the prescribing information i.e. Summary of Product Characteristics (SPC) or data sheet.

However, clinical trial programmes before marketing are limited in their power to detect rare, particularly type B (non-pharmacologically mediated) [6] ADRs. This is because of the limited number of patients that are studied before marketing [7], the frequent exclusion of patients who may be at greater risk e.g. the elderly and those with significant concurrent disease, and the structured nature of clinical trials where drugs are given at specific doses for limited periods

of time by experienced investigators. Only with wider experience after marketing during routine clinical practice and possibly in larger studies will the less common ADRs and other 'at risk' groups be identified. Post-marketing surveillance (PMS) by companies is therefore essential.

Methods of PMS used by the pharmaceutical industry

The general process is basically that utilised by regulatory authorities and other parties working on drug safety matters. The first step is signal generation, i.e. processes that can identify possible new ADRs. There may then be a period of signal strengthening and in the second step such signals are subjected to hypothesis testing, i.e. processes that determine whether the signal does indeed indicate a new ADR, or whether it is false. Whereas the signal generation process is, in principle, relatively simple if the right systems are in place, the hypothesis testing process is challenging and often time consuming and may require a variety of different approaches. The key problem encountered is 'signal *vs* noise'—many adverse events observed in treated patients in the end turn out to be related to factors other than the treatment.

The signal generation process

Signals may be generated through four different methods: spontaneous reporting, published case reports, cohort studies and post-marketing clinical trials.

Spontaneous reporting

Recording and reporting clinical observations of a suspected ADR with a marketed drug is known as spontaneous or voluntary reporting. The national system in the UK is the 'yellow card' scheme where doctors, dentists, and recently, hospital pharmacists are encouraged to report all suspected reactions to new medicines and serious suspected reactions to established medicines. Pharmaceutical companies also collect and collate such reports with their licensed products [8]. Reports to companies often come initially as a question from a prescribing physician or pharmacist to Medical Information or a sales representative about whether a product could be the cause of a patient's problem. After providing such information, pharmacovigilance staff will seek details of the case to add to the database of reports, this relies on the goodwill and continued interest of reporters. Companies must report suspected ADRs to the MCA and other authorities; some authorities, including MCA, make anonymised data available to licence holders. There is also a move towards electronic exchange of data between authorities and companies.

The culture of reporting varies greatly between countries in terms of the quantity, quality and source of reports. In the UK and Sweden most doctors report directly to the national regulatory authority rather than pharmaceutical companies, although some report to both. In other countries such as Germany and the USA the majority of reports go initially to companies who then report to the authority in that country. The proportion of reports received by companies directly from patients also varies considerably between countries and is highest in the USA.

Spontaneous reporting has advantages in that it is available immediately a new product is marketed, continues indefinitely and covers all patients receiving the drug. It is the most likely method of detecting new, rare ADRs and frequently generates safety signals which need to be examined further. The main limitations are the difficulty in recognising previously unknown reactions, particularly events that are not usually thought of as being ADRs and under-reporting, which is variable, sensitive to reporting stimuli and difficult to quantify. It usually does not confirm hypotheses, although situations exist where spontaneous reporting data alone allow conclusions that a signal indeed represents a true ADR, see 'using spontaneous reporting data for hypothesis testing' below.

Published case reports

Publishing case reports of suspected ADRs in medical journals is an established way of alerting others to possible drug hazards. However, it has limitations as only a very small proportion of cases can be published, reports are sometimes poorly documented, publication depends on editorial selection and there is often considerable delay between occurrence and publication. Companies and some regulatory authorities actively monitor the published literature for such reports. This will involve screening key journals where ADRs are described, monitoring publications such as 'Reactions Weekly' (ADIS International) and running regular standard searches on databases such as Medline and Excerpta Medica. With efficient regulatory and company safety surveillance it is now relatively rare for a new ADR to be signalled primarily through published cases, however, publication of well characterised ADRs still fills an important function in alerting physicians. A more recent development is reports of possible ADRs appearing on the Internet and many companies are still determining how they should best handle them.

Cohort studies

Companies may set up or sponsor prospective, non-interventional cohort type studies either to answer safety questions raised after marketing or as a general hypothesis generating and testing tool to be used as need arises. In the past, company sponsored studies were considered poor at detecting new safety issues mainly because of slow recruitment and lack of control groups [9]. Since 1994 such studies in the UK have been subject to the SAMM (Safety Assessment of Marketed Medicines) guidelines [10] which have ensured a closer dialogue between companies and the MCA. Generally, cohort studies are ineffective as tools for signal generation, mainly because of limitations in size, also data from such studies are subject to the 'signal *vs* noise' problem in the same way as spontaneous reports.

Post-marketing clinical trials

Large randomized clinical trials with wide entry criteria (similar to SPC indications) can be valuable in assessing the

safety of marketed products as well as confirming efficacy. Because patients are randomised to different treatments they do not have some of the problems inherent in cohort studies, for instance whether the control group is truly comparable. Companies can choose to set up or sponsor such studies to address particular safety issues. To make them sufficiently large to provide more information than the trials performed for product registration purposes may make them prohibitively expensive, hence a simple protocol and study plan with limited observations is desirable.

The hypothesis testing process

A typical situation in company pharmacovigilance is that a small number of reports have been received, showing that the patients have developed a serious medical condition, e.g. liver function disturbance, convulsions or blood dyscrasia, while receiving a particular product. As much detail as possible on the cases must be obtained and any new cases followed-up rigorously but the hypothesis must be raised that this condition has been caused by the drug, i.e. represents an ADR. For analysis of this question, a number of approaches can be taken, the most common being to use the spontaneous reporting data in a variety of ways. Another is to move into formal epidemiological e.g. case-control studies. Pre-clinical pharmacological and toxicological data and clinical trial experience should also be reviewed.

Using spontaneous reporting data for hypothesis testing

It is commonplace in clinical practice to make decisions and take actions based on assessment of causality between an event and a certain drug in individual cases. General pharmacovigilance experience however, is that determination of causality in individual cases has a high degree of uncertainty. Attempts to develop the methodology for causality assessment, e.g. by using a Bayesian approach have yielded interesting results [11] but has so far had little impact. Some exceptions to this uncertainty exist, however, for instance the situation of positive rechallenge, i.e. that symptoms and objective findings, having disappeared following discontinuation of the treatment, reoccur on renewed exposure. The other situation is when the adverse event in several patients shows a very consistent pattern both in symptomatology and in relation to the duration of treatment before symptoms, e.g. zimeldine and Guillain-Barre syndrome [12].

These points illustrate an important similarity between clinical medicine and pharmacovigilance—there is no substitute for careful observation and analysis of single cases. In special situations, various biochemical markers or pharmacokinetic data in individual patients may also contribute to judgements regarding whether observed symptoms or disorders constitute an ADR.

Sometimes, spontaneous reporting data can be used for comparing frequencies of a certain event in a treated population with background incidence of that event. This may be especially possible for rare conditions, like blood dyscrasias. Although there is a high degree of underreporting, if the reporting rate for a certain event, which can be regarded as a minimum frequency, clearly exceeds the expected frequency, this raises a strong suspicion about a causal relationship. This is a relatively rare occurrence partly because for many conditions reliable background incidence data are not available.

In real life, hypothesis testing can be a rather unsophisticated process. A simple approach is that once the number of reported events of a certain type becomes sufficiently great, regulatory authorities and company pharmacovigilance units could take the stance that these numbers probably reflect a true adverse reaction, unless there exists sufficiently convincing evidence for other causative factors. The general attitude in this area is to an increasing extent being influenced by the fear of litigation, especially in the United States. Most companies now take a very cautious attitude and tend, for legal reasons, to include in the prescribing information a number of possible ADRs which may not have been proven to be real. This is gradually having a more detrimental effect on the value of the prescribing information to practising health care professionals.

Epidemiological studies

During the last decade pharmacoepidemiology, the study of the use and effects of drugs in large populations [13], has emerged as a developing discipline and has made important contributions to our understanding of drug safety. A good example of this is the confirmation and quantification of the relation between NSAID treatment and gastrointestinal ulceration and bleeding [14]. Expertise in pharmacoepidemiology is now a must for any research based pharmaceutical company and there has been a substantial growth of know-how in many over the past few years. In addition, many companies have established research collaborations with academic institutions in pharmacoepidemiology.

Pharmacoepidemiological studies are largely based on observational rather than experimental data and have some important methodological problems, particularly confounding and bias. The recent debate about studies with third generation oral contraceptives is a good example of this. It is possible that the observed differences between third generation oral contraceptives as compared with second generation ones are due to confounding or bias or both rather than on real differences [15, 16], although this is still controversial [17].

There is a general scientific and ethical dilemma in pharmacovigilance, which is related to the major mass media attention that drug risks receive. At what point in time during the evaluation of a potential hazard should information be disseminated? If communication is premature, before a hypothesis has been confirmed, the risk is that patients are deprived of useful medicines. If it is too late, patients may be exposed to unnecessary risks. Obviously, there is no simple answer, each case has to be evaluated separately, taking a great number of factors into account including not only the possible ADR under evaluation, but also the risks with the disorder being treated and the risks with alternative treatments [18] and inappropriate treatment cessation.

This general dilemma, related to media attention, does not only concern pharmaceutical companies but also regulatory authorities and academic institutions involved in

pharmacovigilance. Anyone communicating a possible new risk must now realise that the result may be an immediate global media storm, with wide-ranging consequences. Although open communication and full disclosure are basic principles in pharmacovigilance the impact of going public must be carefully considered.

National and international regulatory requirements

The reporting of safety information from clinical trials and with marketed products by pharmaceutical companies to regulatory authorities has been mandatory for many years but with each national authority having different requirements. Recent attempts have been made to unify reporting under the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [19] which brings together regulatory authorities and other experts from Europe, USA and Japan. However, despite this and European Directives and Regulations there is still diversity in requirements [20] and the guidance from the CPMP Pharmacovigilance Working Party is still in preparation.

The current UK requirements for investigational drugs are included in the CTX/CTC guidance [5] and for licensed products are outlined in the MCA publication Medicines Act Information Letter No 87 [21]. For marketed products individual serious suspected reactions (expedited reports) must be sent to MCA within 15 calendar days of receipt by the company. This applies to UK cases and those from all other European member states; for cases originating outside the EU only serious and unexpected cases (those not listed in the SPC) are subject to expedited reporting. Periodic safety updates containing information on a much wider range of reports and other worldwide safety data over a specified time period are also required. Other EU countries have similar requirements but often differ in detail. If the product is being developed or is marketed in the USA there are extensive FDA reporting regulations with strict deadlines that also have to be met.

One feature of the European requirements is that Marketing Authorisation holders i.e. companies, must have a suitably qualified person responsible for pharmacovigilance. Their responsibilities include the establishment and maintenance of a system which ensures that all ADRs reported to company personnel are collected and collated so that they may be accessed at a single point within the community, the preparation of various reports and answering requests for the provision of additional information from the authorities. Meeting worldwide regulatory reporting requirements is a key business need in pharmacovigilance and companies have invested heavily in staff, computer systems and procedures to meet them. However, this should not overshadow the need for good science and judgement in identifying and analysing important safety issues with products.

Pharmacovigilance is not just about reporting cases to the regulatory authorities, the results of PMS and hypothesis testing should provide useful information which can be communicated to prescribers by updating the SPC/data sheet and Patient Information Leaflet as safety signals are confirmed. Many such updates are initiated by companies although some are imposed by the authorities. The CIOMS III Working Group have compiled a useful commentary and guidance on what core safety information should be available for a product [22].

Issue and crisis management

Normally, the signal generation and hypothesis testing processes are long-term, and continuous throughout the lifetime of a product, resulting in a gradual build-up of knowledge of the safety properties. At times, however, the process has to become very much compressed in time, resulting in a crisis. This may be because a safety signal implies the possibility of a new and important risk, but actions from regulatory authorities and/or mass media activities may also trigger such situations.

The most important characteristic of the crisis situation is shortage of time. A possible serious hazard for patients, the imminent threat of regulatory actions or mass media pressures calls for rapid actions. At the same time there is a need for analysis of all available data, consultations with experts of various kinds, internal discussion within the company, information to various parties and other activities. This situation is normally handled by a task force, where pharmacovigilance expertise is an important part. Typically, a task force has to produce an analysis of all available data, consult with experts, handle internal and external information and, in the end, make considered benefit-risk judgements and propose actions to be taken. This kind of work is the real test of expertise in pharmacovigilance—to work under extreme internal and external pressures against very short timelines.

The future

Pharmacovigilance in the industry will continue to grow and develop as a discipline. In the past, pharmacovigilance units have spent substantial proportions of their time reporting single cases to regulatory authorities around the world, fulfilling widely different local requirements. Current developments promise that this aspect will be gradually simplified. The strong development towards international harmonisation will result in much more uniform international requirements and the very rapid developments in electronic communication will allow automated distribution of case reports within companies and to regulatory authorities.

The future focus of pharmacovigilance work will, therefore, be on the science more than on the formal regulatory aspects, although these, obviously, will continue to be important. Developing and using tools from, for instance, epidemiology and health economics will allow much better judgements of the real impact of treatments on public health and the costs of health care. This fits well with the increasing demand from governments, health care providers and institutional buyers regarding documentation of real benefits of treatments with acceptable risk profiles. The challenge to those working in pharmacovigilance will therefore be to investigate and document, in epidemiological and health economic terms, whether drug safety profiles obtained from clinical trials in narrowly selected populations

still hold true when drugs are used in clinical practice. In addition, the identification of possible rare but serious ADRs, and possible actions to prevent them or minimise their negative impact, will continue to be key tasks.

References

1 CSM & MCA. Pharmacovigilance. *Current Problems in Pharmacovigilance* 1993; **19**: 1.

2 SIGAR. Pharmacovigilance Education and Certification—Report on a Feasibility Survey. *Pharmacoepi & Drug Safety* 1995; **4**: 305–309.

3 Skegg DCG, Doll R. The case for recording events in clinical trials. *Br Med J* 1977; **2**: 1523–1524.

4 Wallander MA. The way towards adverse event monitoring in clinical trials. *Drug Safety* 1993; **8**: 251–262.

5 Medicines Act 1968. Guidance notes on applications for clinical trial exemptions and clinical trial certificates. *MCA*, 1996; 94–99.

6 Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions In *Textbook of adverse drug reactions*, 4th edition, ed. Davis DM, Oxford University Press, 1991, 18–45.

7 Rawlins MD, Jefferys DB. Study of United Kingdom product licence applications containing new active substances, 1987–9. *Br Med J* 1991; **302**: 223–225.

8 Talbot JCC. Spontaneous reporting. In *Drug safety—a shared responsibility*, Edinburgh, Churchill Livingstone, 1991: 37–45.

9 Waller PC, Wood SM, Langman MJS, Breckenridge AM, Rawlins MD. Review of company post marketing, surveillance studies. *Br Med J* 1992; **304**: 1470–1472.

10 MCA, CSM, RCGP, BMA, ABPI. Guidelines for company sponsored Safety Assessment of Marketed Medicines (SAMM guidelines). *Br J Clin Pharmacol* 1994; **38**: 95–97.

11 Lanctot KL, Naranjo CA. Computer-assisted evaluation of adverse events using a Bayesian approach. *J Clin Pharmacol* 1994; **34**: 142–147.

12 Kristoffersson A, Nilsson BS. Zimeldine: febrile reactions and peripheral neuropathy. In *Autoimmunity and Toxicology*, eds Kammüller ME, Bloksma N, Seinen W. Elsevier Science Publishers BC, 1989: 183–214.

13 Strom BL. What is Pharmacoepidemiology? In *Pharmacoepidemiology*, 2nd edition, ed. Strom BL, Wiley, New York, 1994: 3–13.

14 Henry D Lim LY, Rodriguez LAG, *et al*. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *Br Med J* 1996; **312**: 1563–1566.

15 Farmer RDT, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. *Lancet* 1997; **349**: 83–88.

16 Lewis MA, Heinemann LAJ, MacRae KD, Bruppacher R, Spitzer WO. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. The Transnational Research Group on Oral Contraceptives and the Health of Young Women. *Contraception* 1996; **54**: 5–13.

17 Vandenbroucke JP, Rosendaal FR. End of the line for 'third-generation-pill controversy?' *Lancet* 1997; **349**: 1113–1114.

18 Edwards R, Wiholm BE, Martinez C. Concepts in risk-benefit assessment. A simple merit analysis of a medicine? *Drug Safety* 1996; **15**: 1–7.

19 Proceedings of The Third International Conference on Harmonisation Yokohama 1995, eds. D'Arcy PF & Harron DWG, Queens' University of Belfast, 1996.

20 Arnold BDC. A review of the European Community Regulatory Requirements for expedited and periodic ADR reporting. *Drug Inf J* 1997; **31**: 181–186.

21 MAIL 87. *Pharmacovigilance in the new European system*. Medicines Control Agency, January/February 1995.

22 Report of CIOMS (Council for International Organisations of Medical Sciences) Working Group III, Guidelines for Preparing Core Clinical-Safety Information on Drugs, Geneva, 1995.

(*Received 12 September 1997, accepted 6 January 1998*)